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| 09/446,634 | 12/23/1999 | HIROSHI HAGIYA | Q57282 | 2661 |

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| EXAMINER |
|---|
| YU, MISOOK |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 12 |

DATE MAILED: 09/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/446,634 | Applicant(s) HAGIYA ET AL. | |
|---|---|---|---|
| | Examiner Misook Yu | Art Unit 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *5-19, and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election without traverse of group I, claims 1-4 and 28, species the mouse Fas antigen in Paper No. 11 is acknowledged.

Claims 5-19, and 21-23 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Claims 1-4, and 20 are examined on merits as drawn to mouse Fas antigen.

### *Specification*

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 3 depends from claim 2, drawn to a isolated plasmid DNA comprising 136$^{th}$ to 305$^{th}$ positions of mouse Fas and claim 3 is drawn a isolated plasmid DNA comprising 136$^{th}$ to 305$^{th}$ positions of mouse Fasm plus a signal sequence of the Fas, therefore DNA claimed in claim 3 is outside of the limitation of DNA in claim 2.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "a functional region of an Fas antigen" but it is not clear what the metes and bounds are for the phrase. The specification does not define the phrase.

Does the phrase mean death domain of Fas (see Fig. 1 of Takebayashi et al, 15 Sept. 1996, Cancer Research 56, 4164-4170, copy provided as part of the Search Report for PCT/JP98/02785)? Or Does it mean something else?

Claim 3 recites "the signal peptide region" but it is not clear what the metes and bounds are for the phrase. The specification at page 3 lines 13 and 14 says that the 1st to 16th amino acids position of the human Fas is "assumed to be its signal peptide" but the specification does not define what is "the signal peptide region" of mouse Fas antigen.

Claim 4 recites "the "-21st to 14th positions of mouse Fas" but it is not clear what the metes and bound are for the phrase. The specification does not define the amino acid position as signal peptide sequence. In fact the specification at page 3 lines 13 and 14 seems to imply that 1st to 16th amino acids position of the human Fas might be the signal peptide sequence. See rejection claim 3 above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 20 is drawn to a therapeutic agent for treatment of cancer or autoimmune disease comprising a plasmid DNA comprising (1) Gal4 responsive element, UAS, note page 27 the last line (2) a promoter, herpes simplex virus thymidine kinase, note page 27 line 7, and (3) a part of mouse Fas protein defined as a transmembrane region and a functional region more specifically the 136th to 305th amino acids position of mouse Fas which encompasses the transmembrane and death domain or (3) above plus the signal peptide region of Fas. Note page 27 Example 4.

The specification at page 27, Example 4 teaches how to make the plasmid DNA of instant claim 2. The plasmid constructs claimed in instant claims 1-4 does not

encode fusion protein, but the DNA encoding "effector protein" recited in claim 20 encodes fusion protein of yeast Gal4 linked to human PPAR. The specification at Example 3 describes how to make the DNA construct, which encodes yeast Gal4-human PPAR fusion protein. Figures 1-4 of the instant application show that more of the two DNA transfected cells die, compared to control cells in presence of the PPAR activator compounds. The specification in the paragraph bridging pages 31 and 32 interpret the cell death caused by increased expression of Fas cytosolic domain. The synopsis of the event is that the Gal4 part of the fusion protein "the effector protein" binds to UAS site of the DNA construct of claim 2 when the PPAR part of the fusion protein is stimulated by the PPAR activator compounds used in Figs. 1-4, which in turn stimulates expression of Fas cytosolic domain under Gal4 enhancer element and this expression, i.e. Fas cytosolic domain causes cell death.

One cannot extrapolate the teaching of the specification to the claim because it is well known that the art of anticancer drug discovery for cancer therapy or autoimmune disease treatment is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para) and Forre et al (2000, Scand J Rheuatol. Vol. 29, pages 73-84) teach that autoimmune disease is very difficult to treat due to its unknown etiology. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly

possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Further, the specification does not teach how to target the two plasmids into cancer cells in vivo. The specification at page 28 line 9 says that the plasmids are transfected into in vitro L929 cells using Lipofect Amine; this approach has been used in the art to transfect DNA into in vitro cells, not in vivo cells. Note third paragraph of left colum, page 4164 of Takebayashi et al, 15 Sept. 1996, Cancer Research 56, 4164-4170). One in ordinary skill would not accept that the method of in vitro transfection disclosed in the instant specification would target the two plasmids to in vivo cancer cells to treat cancer or autoimmue diseases because it is well known in the art that it is difficult to deliver DNA to target sites. For example, Merdan et al (Adv Drug Deliv Rev Sep 13, 2002 Vol. 54, 715, abstract only) teaches that treating human diseases using gene therapy is desirable but this approach with non-viral vectors still has to overcome. The instant specification does not even teach any in vivo animal model for cancer or autoimmune diseases using tthe two vectors.

The specification provides insufficient guidance, and provides no working examples of a treatment in vivo which would provide guidance to one skilled in the art to

use the claimed invention without undue experimentation, and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed invention with a reasonable expectation of success. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu, Ph.D.
September 3, 2002

MARY E. MOSHER
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